# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicants: | Cohava Gelber and Kathleen Rousseau | | |
| Serial No.: | 10/632,878 | Art Unit: | 1654 |
| Filed: | August 1, 2003 | Examiner: | Ronald T. Niebauer |
| For: | *CELL TRANSPORT COMPOSITIONS AND USES THEREOF* | | |

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Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

## APPEAL BRIEF

Sir:

This is an appeal from the final rejection of claims 1, 3-36 and 38 in the Office Action mailed on April 18, 2007, in the above-identified patent application. A Notice of Appeal was filed on August 20, 2007 with a Petition for Extension of Time for one month. The Commissioner is hereby authorized to charge $510.00, the fee for the filing of an Appeal Brief for a large entity, to Deposit Account No. 50-3129.

It is believed that no additional fee is required with this submission. However, should an additional fee be required, the Commissioner is hereby authorized to charge the fee to Deposit Account No. 50-3129

## (1) REAL PARTY IN INTEREST

The real party in interest of this application is the assignee, MannKind Corporation.

## (2) RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences known to appellant, the undersigned, or appellant's assignee which directly affects, which would be directly affected by, or which would have a bearing on the Board's decision in this appeal.

## (3) STATUS OF CLAIMS

Claims 1, 3-36 and 38 are pending, rejected, and on appeal. Claims 2 and 37 have been cancelled. The text of each claim on appeal, as pending, is set forth in an Appendix to this Appeal Brief.

## (4) STATUS OF AMENDMENTS

An Amendment after the final rejection, in which claim 28 was amended, was filed on August 20, 2007. In the Advisory Action mailed on September 5, 2007, the Examiner indicted that this Amendment would be entered.

A Supplemental Amendment after the final rejection was filed on October 17, 2007, correcting an obvious typographical error in the dependency of claim 11 so that claim 11 depends from claim 38. The Examiner has not yet indicated if this amendment will be entered.

## (5) SUMMARY OF CLAIMED SUBJECT MATTER

Independent claim 1 defines a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, comprising forming a complex comprising the compound and an effective amount of diketopiperazine (DKP) to enhance transport of the

compound directly into the cell, wherein transport of the compound is increased in the presence of the DKP compared to in the absence of the DKP, and contacting the cell *in vivo* with the complex (*see* page 2, lines 1-10 and from page 3, line 27 until page 4, line 1).

Dependent claim 3 specifies that the DKP is coated with a synthetic or natural polymer (*see* page 4, line 2).

Dependent claim 5 specifies that the compound is a biologically active agent (*see* page 4, line 20). Dependent claim 6 specifies that the biological agent is insulin, an insulin precursor, Parathyroid hormone (PTH), Calcitonin, Human Growth Hormone (HgH), a Glucagon-like peptide (GLP), a cytokine, a chemokine, or a fragment thereof (*see* page 4, lines 26-29). Dependent claim 7 depends from claim 5, and specifies that the biologically active agent is an antibody or fragment thereof (*see* page 4, lines 26-29).

Dependent claim 8 specifies that the diameter of the complex is less than 5 microns (*see* page 8, lines 14-16). Dependent claim 9 specifies that the diameter of the complex is less than 2.5 microns (*see* page 8, lines 18-19). Dependent claim 10 specifies that the diameter of the complex is between 1.5 and 2.5 microns (*see* page 8, line 19).

Claim 13 depends from claim 1, and specifies that the DKP does not engage a toll-like receptor (*see* page 4, lines 10-11).

Dependent claim 14 specifies that the cell is in a pulmonary tissue (*see* page 10, line 8). Dependent claim 15 requires that the pulmonary tissue comprises a small airway of the lung *see* page 10, lines 16-17. Dependent claim 16 requires that the pulmonary tissue comprises alveoli (*see* page 10, lines 16-17).

Dependent claim 17 depends from claim 14, and specifies that the dosage of the composition is between 0.5 and 100 milligrams per administration (*see* page 9, lines 1-2). Dependent claim 18 specifies that the dosage of the compound is between 500 and 1000 micrograms per administration (*see* page 9, lines 2-3). Dependent claim 19 specifies that the dosage of the compound is between 2-16 milligrams per day (*see* page 9, lines 4-5).

Dependent claim 20 depends from claim 14, and specifies that the molecular weight of the compound is less than 200 kDa (*see* page 8, lines 21-22). Dependent claim 21 specifies that the molecular weight of the compound is less than 100 kDa (*see* page 8, line 22); Dependent claims 22 and 23 specify that the molecular weight of the compound it is less than 50 kDa or between 3 and 6 kDa, respectively (*see* page 8, lines 23-25).

Dependent claim 28 depends from claim 14, and specifies that the contact step is repeated (*see* page 10, line 22-23). Dependent claim 29 specifies that the time interval between the contacting steps is less than 24 hours (*see* page 10, lines 23-24). Dependent claim 30 specifies that the time interval between the contacting steps is less than 12 hours (*see* page 10, line 25). Dependent claim 31 specifies that the time interval between the contacting steps is less than 6 hours (*see* page 10, lines 25-26). Dependent claim 32 specifies that the time interval between the contacting steps is or less than 3 hours (*see* page 10, line 26). As required by dependent claim 33, following the plurality of contacting steps, immune cells in the pulmonary tissue are non-responsive to subsequent contact with the compound (*see* page 10, line 26-28).

Dependent claim 24 specifies that the compound is a polypeptide (*see* page 4, lines 23-26). Dependent claim 25 specifies that the amino acid sequence of the polypeptide is identical to a naturally occurring polypeptide expressed by a member of the species of the mammal (*see* page

4, lines 23-26). Dependent claim 26 specifies that the polypeptide is insulin, an insulin precursor, Parathyroid hormone (PTH), Calcitonin, Human Growth Hormone (HgH), a Glucagon-like peptide (GLP), or a fragment thereof (*see* page 4, lines 26-29). Dependent claim 27 specifies that the polypeptide is an antibody or a fragment thereof (*see* page 4, lines 26-29).

Claim 34 depends from claim 1, and specifies that the cell is located in a mammal (*see* page 4, lines 25-26). Dependent claim 35 specifies that the mammal is a human (*see* page 9, lines 4-5). Dependent claim 36 depends from claim 34, and specifies that the composition is administered orally (*see* page 10, lines 17-18).

Dependent claim 38 specifies that the cell is contacted with the complex in a schedule resulting in substantially no increase in the cell's immune response (*see* page 11, lines 5-7). Dependent claim 4 depends from claim 38, and specifies that the immune response is increased by less than 20% in the presence of DKP compared to in its absence (*see* page 4, lines 5-6).

Dependent claim 11 depends from claim 3, and specifies that the immune response is measured by detecting an antibody, T cell proliferation, or production of a cytokine (*see* page 4, lines 6-7). In the Amendment filed on October 17, 2007, the dependency of claim 11 was corrected so that claim 11 depends from claim 38. Dependent claim 12 depends from claim 11, and specifies that the cytokine is interleukin-2 (*see* page 4, lines 6-7).

## (6) GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The issues presented on appeal are:

(i) whether claims 1, 3-6, 8-18, 20-24, 26, 28, 33-36 and 38 are anticipated under 35 U.S.C. §102(b) by U.S. Patent No. 6,071,497 to Steiner, *et al.* ("the "497 patent").

(ii) whether claims 1, 4-10, and 13-36 are anticipated under 35 U.S.C. §102(e) by U.S. Patent No. 6,652,885 to Steiner, *et al.,* ("the '885 patent"); and

(iii) whether claims 1, 3-36 and 38 are obvious under 35 U.S.C. §103(a) over the '497 patent in view of the '885 patent.

## (7) ARGUMENTS

### (a) The Claimed Invention

Many therapeutic compounds are not clinically useful for commercial development because they are soluble in aqueous environments by not sufficiently soluble in non-polar environments. Such compounds can travel through an aqueous environment to reach target cells, but then cannot reach an intracellular target, because of the difficulties in crossing the non-polar lipid bilayer of a cell. Thus, standard means of drug administration are limited in their efficiency and ability to target certain tissues. Additionally, some drug delivery agents produce undesirable side effects, such as inflammation and toxicity.

The claims define a method for enhancing transport of compounds across the membrane of a cell containing a lipid bilayer. The claimed method requires forming a complex comprising the compound to be delivered and an effective amount of diketopiperazine (DKP) to enhance transport of the compound directly into the cell.

### (b) Rejections Under 35 U.S.C. § 102(b)

#### ***Legal Standard***

For a rejection of claims to be properly founded under 35 U.S.C. § 102, it must be established that a prior art reference discloses each and every element of the claims. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 231 USPQ 81 (Fed. Cir. 1986); *Scripps*

*Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565, 18 USPQ2d 1001 (Fed. Cir. 1991).

The Federal Circuit held in *Scripps*, 18 USPQ2d at 1010:

> Invalidity for anticipation requires that all of the elements and limitations of the claim are found within a single prior art reference. There must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of the invention.

A reference that fails to disclose even one limitation will not be found to anticipate, even if the missing limitation could be discoverable through further experimentation. As the Federal Circuit held in *Scripps*, *Id.*:

> [A] finding of anticipation requires that all aspects of the claimed invention were already described in a single reference: a finding that is not supportable if it is necessary to prove facts beyond those disclosed in the reference in order to meet the claim limitations. The role of extrinsic evidence is to educate the decision-maker to what the reference meant to persons of ordinary skill in the field of the invention, not to fill in the gaps in the reference.

For a prior art reference to anticipate a claim, it must enable a person skilled in the art to make and use the invention. "A claimed invention cannot be anticipated by a prior art reference if the allegedly anticipatory disclosures cited as prior art are not enabled". *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 314 F.3d 1313, 1354, 65 USPQ2d 1385, 1416 (Fed. Cir. 2003).

***Analysis***

***The '497 Patent***

*(i) Claims 1, 3, 5-6, 8-10, 14-18, 20-24, 26, 28, and 34-36 are novel over the '497 patent.*

The '497 patent discloses a drug delivery system containing a diketopiperazine and drug to be delivered. The '497 patent discloses administration of the drug to the pulmonary system (*see e.g.* abstract).

The '497 patent does not disclose the claimed method, which includes forming a complex comprising the compound and an effective amount of DKP to enhance transport of the compound directly into the cell. The Examiner points to Example 1 of the '497 patent in support of his rejection (Office Action mailed April 28, 2007, page 5, first full para.). In Example 1, the '497 patent discloses a study of the administration of salmon calcitonin (sCT)-diketopiperazine microparticles to sheep. Following instillation of the microparticles in each lung of the sheep, the blood was sampled, collected, and analyzed to determine that blood plasma concentrations of sCT. These results were compared to the blood plasma concentrations of sCT obtained following subcutaneous injection of sCT. The results showed rapid absorption of sCT into blood plasma following administration to the lung and via subcutaneous injection (col. 11, lines 62-64). A discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. As discussed in, Patton, *et al.*, "The Lungs as a Portal of Entry for Systemic Drug Delivery", *Proc. Amer. Thorac. Soc.*, 1:338-344 (2004) ("Patton") (submitted with the Amendment and Response filed on January 5,

2007, a copy of which is attached to the Evidence Appendix), the "precise mechanisms of macromolecule absorption in the lungs are not well known." (*Id.*, page 341, right col., first full para.) Patton indicates that generally "exogenous macromolecules are thought to be absorbed from the airspaces nonspecifically". (*Id.*) Thus, the mere disclosure in the '497 patent regarding the blood serum levels of calcitonin does not disclose or suggest administration into a cell, let alone that a complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer.

However, the Examiner alleges that the '497 patent discloses administration of microparticles into a cell (Office Action mailed on April 18, 2007, page 5, *citing* the '497 patent, col. 10, line 14). Appellants respectfully disagree. Col. 10, lines 14-15 of the '497 patent states that the microparticles can be delivered to specific cells, especially phagocytic cells and organs and notes that phagocytic cells selectively take up microparticles. Uptake of compound by phagocytic cells is not equivalent to transport of a compound across a cell membrane. Similarly, the '497 patent's disclosure at col. 10, lines 23-28 of attaching the microparticle to ligands, such as antibodies or hormones, which specifically or non-specifically bind to particular targets via binding to their receptors on the surface of the cell is not equivalent to a disclosure of enhanced transport across a cell membrane and into the cell. Therefore, claims 1, 3, 5-6, 8-10, 14-18, 20-24, 26, 28, and 34-36 are novel over the '497 patent.

*(ii) Claims 4, 11-12, 33, and 38 are novel over the '497 patent.*

In addition to the reasons discussed above with respect to claims 1, 3, 5-6, 8-10, 14-18, 20-24, 26, 28, and 34-36, the '497 patent does not disclose the method defined by claims 4, 11-12 and 38 for at least the following additional reasons.

Claim 38 depends from claim 1 and further specifies that the cell is contacted with the complex in a schedule resulting in substantially no increase in the cell's immune response. Claim 4 depends from claim 38 and recites that the immune response is increased by less than 20% in the presence of DKP compared to in its absence. Claim 11 specifies that the immune response is measured by detecting and antibody, T cell proliferation or production of a cytokine. An After final Amendment was filed on October 17, 2007, correcting an obvious typographical error in the dependency of claim 11 so that claim 11 depends from claim 38. Claim 12 depends from claim 11, and specifies that the cytokine is interleukin-2.

Claim 33 depends from claim 28, which depends from claim 14, and additionally specifies that following the plurality of contacting steps, immune cells in the pulmonary tissue are non-responsive to subsequent contact with the compound.

The '497 patent contains no disclosure relating to preventing an increase in a cell's immune response, much less how to achieve this.

The present Examiner indicated that he was continuing to reject the claims based on the reasons set forth in the previous Office Actions and for the additional reasons recited in the Office Action mailed April 18, 2007 (Office Action mailed April 28, 2007, page 4, first full para.). The prior Examiner acknowledged that "the '497 patent only addresses the issue of intentionally increasing the immune response when there is an antigen involved as an active agent. There is no mention of immunological issues outside of that specific arrangement of components in that one possible composition ([the '497 patent, at] column 9). Therefore, it is inferred that there are not particular concerns with immunological responses in the '497 patent when one skilled in the art is using the calcitonin/DKP compound of the '497 patent which is

also instantly claimed." (Office Action mailed on August 24, 2006, page 3) Claim 38 and its dependent claims specify that there is substantially "no increase in the cell's immune response". Similarly, claim 33 specifies that "immune cells in the pulmonary tissue are non-responsive to subsequent contact with the compound." In contrast, as acknowledge in prior Office Actions, the '497 patent is generally not directed to immunological issues. Further, to the extent that the '497 patent contains any disclosure relating to a cell's immune response, the '497 patent teaches away from not increasing a cell's immune response since it discloses methods for **increasing** a cell's response by delivering an antigen. Therefore, in addition to the reasons discussed above with respect to claims 1, 3, 5-6, 8-10, 14-18, 20-24, 26, 28, and 34-36, claims 4, 11-12, 33, and 38 are novel over 'the 497 patent.

*(iii) Claim 13 is novel over the '497 patent.*

Claim 13 depends from claim 1, and additionally specifies that the DKP does not engage a toll-like receptor. The '497 patent contains no disclosure relating to the engagement or lack thereof of a DKP with a toll-like receptor. Therefore, in addition to the reasons discussed above with respect to claims 1, 3, 5-6, 8-10, 14-18, 20-24, 26, 28, and 34-36, clam 13 is novel over the '497 patent.

***The '885 patent***

*(i) Claims 1, 5-10, 14-27, 29-32 and 34-36 are novel over the '885 patent.*

The '885 patent describes a method for purifying peptides and proteins by incorporating them into diketopiperazines to facilitate removal of one or more impurities.

The '885 patent does not disclose the claimed method, which includes forming a complex comprising the compound and an effective amount of DKP to enhance transport of the

compound directly into the cell. Like the '497 patent discussed above, the '885 patent discloses blood levels of drug, such as insulin, following administration, such as via inhalation, and compares these levels with the levels achieved following subcutaneous injection with the drug. (*see e.g.* col. 10, line 62 until col. 11, line 3). However, a discussion of blood plasma levels does not disclose or suggest administration of a compound through a cell membrane and directly into the cell. For example, drug transfer from the lung to the blood in the cephalic vein, may occur via transport between cells. As discussed in Patton, the "precise mechanisms of macromolecule absorption in the lungs are not well known." (*Id.*, page 341, right col., first full para.) Patton indicates that generally "exogenous macromolecules are thought to be absorbed from the airspaces nonspecifically". (*Id.*) Thus, the mere disclosure in the '885 patent regarding the blood serum levels of insulin does not disclose or suggest administration into a cell, let alone that a complex containing the compound to be delivered and DKP can enhance transport through a cell membrane containing a lipid bilayer. Therefore, claims 1, 5-10, 14-27, 29-32 and 34-36 are novel over the '497 patent.

*(ii) Claims 4, 11-12 and 33 are novel over the '497 patent.*

Claim 4 depends from claim 38 and recites that the immune response is increased by less than 20% in the presence of DKP compared to in its absence. Claim 11 specifies that the immune response is measured by detecting and antibody, T cell proliferation or production of a cytokine. An After final Amendment was filed on October 17, 2007, correcting an obvious typographical error in the dependency of claim 11 so that claim 11 depends from claim 38. Claim 12 depends from claim 11, and specifies that the cytokine is interleukin-2.

Claim 33 depends from claim 28, which depends from claim 14, and additionally specifies that following the plurality of contacting steps, immune cells in the pulmonary tissue are non-responsive to subsequent contact with the compound. There is nothing in 'the 885 patent about avoiding an immune response, much less how to achieve this. Therefore, in addition to the reasons discussed above with respect to claims 1, 5-10, 14-27, 29-32 and 34-36, claims 4, 11-12 and 33 are novel over the '885 patent.

*(iii) Claim 13 is novel over the '885 patent.*

Claim 13 depends from claim 1, and additionally specifies that the DKP does not engage a toll-like receptor. The '885 patent contains no disclosure relating to the engagement or lack thereof of a DKP with a toll-like receptor. Therefore, in addition to the reasons discussed above with respect to claims 1, 5-10, 14-27, 29-32 and 34-36, clam 13 is novel over the '885 patent.

**(c) Rejection Under 35 U.S.C. § 103**

Claims 1, 3-36 and 38 were rejected under 35 U.S.C. § 103(a) as obvious over the '497 patent in view of the '885 patent.

***The Legal Standard***

Obviousness is a legal conclusion based on underlying facts of four general types, all of which must be considered by the examiner: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed invention and the prior art; and (4) any objective indicia of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18, 148 USPQ 459 (1966). This standard was recently affirmed by the Supreme Court in *KSR Int'l Co. v. Teleflex, Inc.*, 127 S. Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

The Court recognized that a showing of "teaching, suggestion, or motivation" to combine the prior art to meet the claimed subject matter could provide a helpful insight in determining whether the claimed subject matter is obvious under 35 U.S.C. § 103(a). Indeed, the examiner's attention is drawn to the following quote by the Court in *KSR*:

> The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. [ . . .] There is no necessary inconsistency between the [TSM] test and the *Graham* analysis.

*KSR*, 127 S. Ct. at 1727.

The obviousness analysis requires looking at the invention as a whole. "Focusing on the obviousness of substitutions and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Sons, Inc.*, 919 F.2d 720, 724, 16 U.S.P.Q.2d 1923 (Fed. Cir. 1990); *see Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1383, 231 U.S.P.Q. 81, 93 (Fed. Cir. 1986).

Hindsight analysis, such as picking and choosing from prior art references using the claimed invention as a template, has long been forbidden. *See e.g. In re Fine*, 837 F.2d 1071, 1075 (Fed. Cir. 1988), stating "One cannot use hindsight reconstruction to pick and choose

among isolated disclosures on the prior art to deprecate the claimed invention." In *KSR*, the Court also warned against the use of hindsight analysis in making an obviousness determination. The Court stated, "A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning." (*KSR*, 127 S. Ct. at 1742, citing *Graham*, 383 U.S. at 36 (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into the use of hindsight'" (quoting M*onroe Auto Equipment Co. v. Heckethorn Mfg. & Supply Co.*, 332 F.2d 406, 412, 141 U.S.P.Q. 549 (6th Cir. 1964))).

In response to the *KSR* decision, the Deputy Commissioner for the USPTO issued a memorandum stating: "[I]n formulating a rejection under 35 U.S.C. § 103(a) based upon a combination of prior art elements, it remains necessary to identify the reason why a person of ordinary skill in the art would have combined the prior art elements in the manner claimed." Memorandum from Margaret A. Focarino to Technology Center Directors (May 3, 2007).

***Analysis***

As discussed above, the Court recently reaffirmed the *Graham* factors, which are analyzed below:

***(a) Determining the scope and contents of the prior art***

The scope of the '497 patent and the '885 patent are discussed above.

***(b) Ascertaining the differences between the prior art and the claims***

***(i) Claims 1, 3, 5-10, 14-16, 20-27 and 34-36***

As discussed above with respect to the novelty of the claims, neither the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a cell

membrane comprising a lipid bilayer, much less how to administer a drug directly to a cell. Therefore, since neither of the references alone discloses at least these elements of the claimed methods, the combination of the '497 patent with the '885 patent does not disclose all of the elements of the claimed methods.

*The cited references do not provide one of skill in the art with a reasonable expectation of success*

The '497 and the '885 patents disclose drug transport through an organ membrane, such as the lung, into the blood stream. The fact that transport of the drug occurred from the lungs into the blood stream does not explicitly or inherently amount to a disclosure of transport into a cell through the cell's membrane. As described in Patton, transport into the blood stream occurs through different paths, including between cells. Therefore, one of ordinary skill in the art is not provided with a reasonable expectation of success that a complex of compound and DKP can result in enhanced transport of the compound across a cell membrane and directly into a cell based on the disclosures in the '497 patent and the '885 patent.

***(ii) Claims 4, 11-12, 33, and 38***

As noted above with respect to the novelty of the claims, the '497 patent contains no disclosure relating to preventing an increase in a cell's immune response, much less how to achieve this. As acknowledged in prior Office Actions, the '497 patent is generally not directed to immunological issues. Further, to the extent that the '497 patent contains any disclosure relating to a cell's immune response, the '497 patent ***teaches away*** from not increasing a cell's immune response since it discloses methods for **increasing** a cell's response by delivering an antigen..

Similarly, the '885 patent lacks any disclosure relating to preventing an increase in a cell's immune response, much less how to achieve this.

***(iii) Claim 13***

As discussed above with respect to the novelty of the claims neither the '497 patent nor the '885 patent contains any disclosure relating to the engagement or lack thereof of a DKP with a toll-like receptor. .

***(c) Resolving the level of ordinary skill in the art***

One of ordinary skill in the art at the time of the earliest priority date would likely have experience ranging from a master's degree in pharmaceutical chemistry or pharmaceutical science, with approximately five years or more experience, to a Ph.D. in pharmaceutical chemistry or pharmaceutical science with approximately three years or more experience.

***(d) Evaluating evidence of secondary considerations***

Secondary considerations to be considered include commercial success, long felt but unresolved needs, failure of others, etc.

There are many problems with delivery of therapeutic compounds, such as limited solubility (*see* Specification, page 1, lines 12-18). For example, water soluble compounds can travel though an aqueous environment to reach target cells, but cannot reach intracellular targets because of an inability to cross the lipid bilayer of the cell. Additionally, some drug delivery agents produce undesirable side effects such as inflammation and toxicity.

These problems have been addressed by the claimed methods, which deliver compounds directly into cells by forming a complex of a DKP and the compound to be delivered. This results in increased transport of the compound in the presence of the DKP compared to in the

absence of the DKP. The claimed methods also provide for transport of the compounds across a cell membrane without increasing the cell's immune response.

*Conclusion*

Application of the *Graham* factors demonstrates a combination of the '497 patent and the '885 patent does not make obvious the claimed methods.

***(i) Claims 1, 3, 5-10, 14-16, 20-27 and 34-36***

The '497 patent discloses drug delivery systems containing a DKP and a drug to be delivered. The '885 patent discloses methods for purifying peptides and proteins by incorporating them into diketopiperazines. Neither the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, much less how to administer a drug directly to a cell. Further, the disclosures in the '497 and the '885 patents relating to drug transport through an organ membrane, such as the lung, and into the blood stream, do not make the claimed methods obvious. As described in Patton, transport into the blood stream occurs through different paths, including between cells. Therefore, the combination of the '497 patent and the '885 patent does not make claims 1, 3, 5-10, 14-16, 20-27, and 34-36 obvious.

***(ii) Claims 4, 11-12, 33, and 38***

In addition to the reasons discussed above with respect to the non-obviousness of claims 1, 3, 5-10, 14-16, 20-27, and 34-36, claims 4, 11-12, 33, and 38 are non-obvious for at least the following additional reasons. Neither, the '497 patent nor the '885 patent contain any disclosure relating to preventing an increase in a cell's immune response, much less how to achieve this. Further, to the extent that the '497 patent contains any disclosure relating to a cell's immune

response, the '497 patent ***teaches away*** from not increasing a cell's immune response since it discloses methods for **increasing** a cell's response by delivering an antigen.. Therefore the combination of the '497 patent with the '885 patent would not make claims 4, 11-12, 33, and 38 obvious.

***(iii) Claim 13***

In addition to the reasons discussed above with respect to the non-obviousness of claims 1, 3, 5-10, 14-16, 20-27, and 34-36, claim 13 is non-obvious for at least the following additional reason. Neither the '497 patent nor the '885 patent contains any disclosure relating to the engagement or lack thereof of a DKP with a toll-like receptor. Therefore the combination of the '497 patent with the '885 patent would not make claim 13 obvious.

## (8) SUMMARY AND CONCLUSION

Neither the '497 patent nor the '885 patent disclose or suggest a method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, much less how to administer a drug directly to a cell, as required by claim 1 and its dependent claims. Further, the Examiner has provided no reason why one of ordinary skill in the art would be motivated to modify the '497 patent and/or the '885 patent to arrive at the claimed methods. Further neither the '497 patent nor the '885 patent contains any disclosure relating to how to prevent an increase in a cell's immune response, as required by claims 4, 11, 12, 22, and 38. Additionally, neither the '497 patent nor the '885 patent contains any disclosure relating to the engagement or lack thereof of a DKP with a toll-like receptor, as required by claim 13.

For the foregoing reasons, Appellant submits that claims 1, 3-36 and 38 are patentable.

Respectfully submitted,

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Date: October 22, 2007

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## Claims Appendix

1. (Previously presented) A method for enhancing transport of a compound across a cell membrane comprising a lipid bilayer, comprising forming a complex comprising the compound and an effective amount of diketopiperazine (DKP) to enhance transport of the compound directly into the cell, wherein transport of the compound is increased in the presence of the DKP compared to in the absence of the DKP,

and contacting the cell *in vivo* with the complex.

2. (Canceled) .

3. (Previously presented) The method of claim 1, wherein the DKP is coated with a synthetic or natural polymer.

4. (Previously presented) The method of claim 38, wherein the immune response is increased by less than 20% in the presence of DKP compared to in its absence.

5. (Original) The method of claim 1, wherein the compound is a biologically active agent.

6. (Original) The method of claim 5, wherein the biologically active agent is selected from the group consisting of insulin, an insulin precursor, Parathyroid hormone (PTH), Calcitonin, Human Growth Hormone (HgH), Glucagon-like peptides (GLP), cytokines, chemokines, and fragments thereof.

7. (Original) The method of claim 5, wherein the biologically active agent is an antibody or fragment thereof.

8. (Original) The method of claim 1, wherein the diameter of the complex is less than 5 microns.

9. (Original) The method of claim 1, wherein the diameter of the complex is less than 2.5 microns.

10. (Original) The method of claim 1, wherein the diameter of the complex is between 1.5 and 2.5 microns.

11. (Original) The method of claim 3, wherein the immune response is measured by detecting an antibody, T cell proliferation, or production of a cytokine.

12. (Original) The method of claim 11, wherein the cytokine is interleukin-2.

13. (Original) The method of claim 1, wherein DKP does not engage a toll-like receptor.

14. (Previously presented) The method of claim 1, wherein the cell is in a pulmonary tissue.

15. (Original) The method of claim 14, wherein the pulmonary tissue comprises a small airway of the lung.

16. (Original) The method of claim 14, wherein the tissue comprises alveoli.

17. (Original) The method of claim 14, wherein a dose of the compound is between 0.5 and 100 milligrams per administration.

18. (Previously presented) The method of claim 14, wherein a dose of the compound is between 500 and 1000 micrograms per administration.

19. (Original) The method of claim 14, wherein a dose of the compound is between 2 and 16 milligrams per day.

20. (Original) The method of claim 14, wherein the molecular weight of the compound is less than 200 kDa.

21. (Original) The method of claim 14, wherein the molecular weight of the compound is less than 100 kDa.

22. (Previously presented) The method of claim 14, wherein the molecular weight of the compound is less than 50 kDa.

23. (Original) The method of claim 14, wherein the molecular weight of the compound is between 3 and 6 kDa.

24. (Previously presented) The method of claim 14, wherein the compound is a polypeptide.

25. (Original) The method of claim 24, wherein the amino acid sequence of the polypeptide is identical to a naturally-occurring polypeptide expressed by a member of the species of the mammal.

26. (Previously presented) The method of claim 24, wherein the polypeptide is selected from the group consisting of insulin, an insulin precursor, Parathyroid hormone (PTH), Calcitonin, Human Growth Hormone (HgH), Glucagon-like peptides (GLP), and fragments thereof.

27. (Original) The method of claim 24, wherein the polypeptide is an antibody or fragment thereof.

28. (Previously presented) The method of claim 14, wherein the contacting step is repeated.

29. (Original) The method of claim 28, wherein an interval of time between the contacting steps is less than 24 hours.

30. (Original) The method of claim 29, wherein the interval is less than 12 hours.

31. (Original) The method of claim 29, wherein the interval is less than 6 hours.

32. (Original) The method of claim 29, wherein the interval is less than 3 hours.

33. (Original) The method of claim 28, wherein following the plurality of contacting steps, immune cells in the pulmonary tissue are non-responsive to subsequent contact with the compound.

34. (Previously presented) The method of claim 1, wherein the cell is located in a mammal.

35. (Original) The method of claim 34, wherein the mammal is a human.

36. (Original) The method of claim 34, wherein the complex is administered orally.

Claim 37. (Canceled)

38. (Previously presented) The method of claim 1, wherein the cell is contacted with the complex in a schedule resulting in substantially no increase in the cell's immune response.

## Evidence Appendix

Patton, et al., "The Lungs as a Portal of Entry for Systemic Drug Delivery", *Proc. Amer. Thorac. Soc.*, 1:338-344 (2004) (originally submitted with the Amendment and Response filed January 5, 2007).

## Related Proceedings Appendix

None.